DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
BETHESDA, MARYLAND 20014

Donald Kennedy, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Kennedy:

Enclosed is the Final Report of the Panel on Review of Bacterial Vaccines and Bacterial Toxoids. The Panel has intensively studied all products assigned to it and has made numerous recommendations which it believes should benefit the people who use these products. There was unanimous agreement on most of the recommendations. Rarely, the Panel's recommendation on a minor issue is not unanimous, and this is indicated by a split vote or dissenting statement.

We appreciate the privilege of serving the Food and Drug Administration and hope that our efforts will contribute to the improvement of the drug regulatory process and to the welfare of the people who use these regulated products.

Respectfully submitted,

Gene H. Stollerman, M.D., Chairman
Date: April 10, 1979

Hjordis M. Foy, M.D.
Date: May 15 1979

Geoffrey Edsall, M.D.
Date: 4/27/79

Edward A. Mortimer, Jr., M.D.
Date: April 30 1979

Theodore C. Eickhoff, M.D.
Date: April 23, 1979

Jay P. Sanford, M.D.
Date: 5 June 1979

John C. Feeley, Ph.D.
Date: May 7, 1979

POP-0067

RPT002

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

This is an unedited version of a report prepared by the Panel on Review of Bacterial Vaccines and Bacterial Toxoids, which was submitted to the Food and Drug Administration on approximately August 2, 1979. The views expressed in this document have not yet been evaluated by the Food and Drug Administration. This document is subject to format and editorial changes prior to publication in the Federal Register. These changes are designed to assure that the document is free of incidental errors and conforms to the stylistic requirements established for documents published in the Federal Register.

[PROPOSAL]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

[21 CFR PARTS 610 and 650]

[DOCKET NO. 75 ]



# BACTERIAL VACCINES AND TOXOIDS

## IMPLEMENTATION OF EFFICACY REVIEW

AGENCY: Food and Drug Administration.

ACTION: Proposal.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations in response to the report and recommendations of the Advisory Review Panel on Review of Bacterial Vaccines and Toxoids. The Panel reviewed the safety, efficacy, and labeling of bacterial vaccines and toxoids with standards of potency, antitoxins and immune globulins. Additionally, on the basis of the Panel's findings and recommendations, the Commissioner of Food and Drugs is announcing his conclusion of those products which are in Category II (unsafe, ineffective or misbranded) and Category IIIB (off the market pending completion of studies permitting a determination of effectiveness). Elsewhere in this publication the Commissioner is publishing a notice of opportunity for hearing to revoke the licenses for products in Category II and IIIB.

The Commissioner is also announcing his conclusion as to those products in Category I (safe, effective, and not misbranded) and Category IIIA (on the market during further studies in support of effectiveness) and by this proposal is inviting comments and the submission of views and additional data on the status of these products. In addition, the

The Commissioner is proposing certain amendments to the biologic regulations to incorporate the criteria of safety and effectiveness applied by the Panel and other specific suggestions contained in the Panel Report, and inviting comments on these proposed amendments.

DATES: Comments by (insert date 60 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written comments to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Steve Falter,
Bureau of Biologics (HFB-620),
Food and Drug Administration,
Department of Health, Education, and Welfare,
8800 Rockville Pike,
Bethesda, MD 20014,
(301-443-1306).

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of February 13, 1973 (38 FR 4319), the Commissioner issued § 601.25 (21 CFR 601.25) concerning procedures for review of safety, effectiveness, and labeling of biological products licensed prior to July 1, 1972. The biological products reviewed were assigned, pursuant to a redesignation of panel assignments published in the FEDERAL REGISTER of June 19, 1974 (39 FR 21176), to one of the following categories: (a) Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency," (b) Bacterial Vaccines and Toxoids with Standards of Potency, (c) Viral Vaccines and Rickettsial Vaccines, (d)

Allergenic Extracts, (e) Skin Test Antigens, and (f) Blood and Blood Derviatives.

Pursuant to § 601.25, the Commissioner assigned responsibility for the initial review of each of the biological product categories to a separate independent advisory panel consisting of qualified experts to insure objectivity of the review and public confidence in the use of these products. The Commissioner charged each Panel to (1) evaluate the safety and effectiveness of the biological product, (2) review the labeling of the biological product, and (3) advise him on which biological products under review are safe, effective, and not misbranded, in the form of an advisory review panel report to the Commissioner. The advisory review panel report is to include a statement classifying products into one of three categories.

Category I designates those biological products determined by the Panel to be safe, effective, and not misbranded. The Panel statement may include any condition relating to active components, labeling, tests required prior to release of batches, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

Category II designates those biological products determined by the Panel to be unsafe or ineffective or to be misbranded.

Category III designates those biological products determined by the Panel not to fall within either Category I or II on the basis of the Panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. Those biological products in Category III for which continued

licensing, manufacturing, and marketing are recommended are designated as Category IIIA. Those biological products in Category III for which suspension of the licenses is recommended (and thus denying continuing manufacturing and marketing) are designated as Category IIIB. The recommendation for either Category IIIA or IIIB is based on assessment of the present evidence of safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time, while questions raised concerning the products are being resolved by further study.

For some Category III products, it is the Panel's conclusion that it was not possible to classify them because of essentially administrative problems rather than because of scientific questions. For example, some licenses have been held for products which the manufacturer had not produced or marketed for many years. Other licenses are held for products for which there has never been any labeling; for which the product was not marketed; and which were manufactured only for combination with other biologically active components. The advisory review panel report has designated such products as Category IIIC and recommends that the status of such products should be resolved on the basis of FDA administrative and policy actions.

Although the Panel must, at this time, recommend that licenses be revoked for products placed in Category IIIC because the Panel has been unable to determine what the benefit-to-risk assessment for such products either is or would be if the product became available, it must be noted that the Panel would prefer that some of these products remain

available if FDA administrative actions can satisfactorily resolve information deficiencies.

To facilitate review of safety, effectiveness, and labeling of these products and to provide all interested persons an opportunity to present, for consideration by the Panel, the best information available to support the stated claims for Bacterial Vaccines and Toxoids with Standards of Potency, the Commissioner solicited, in the FEDERAL REGISTER of February 28, 1973 (38 FR 5358), submission of data pertinent to these products.

Subsequent to this, because of a realignment in the number of biological products advisory review panels to be established (39 FR 21176), a request for data and information regarding the safety and effectiveness of antitoxins, immune globulins and other products to be considered by the Panel was published in the FEDERAL REGISTER on June 19, 1974 (39 FR 21176).

Data and information submitted pursuant to the February 28, 1973, and June 19, 1974, notices and falling within the provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j) have been handled as confidential. However, with the publication of this proposed implementation and the full report of the Panel, such data and information will, pursuant to § 601.25(b)(2), be made publicly available (insert date 30 days after publication) and may be viewed at the office of the Hearing Clerk except to the extent that the person submitting the data and information demonstrates that it still falls within one or more of the confidentiality provisions. Accordingly, comments concerning confi-

dentiality should be submitted by (insert 30 days from date of publication).

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of bacterial vaccines, toxoids, related antitoxins and immune globulins:

Panel Chairman, Gene H. Stollerman, M.D., Goodman, Professor and Chairman, Department of Medicine, University of Tennessee College of Medicine, Memphis, TN 38163.

Geoffrey Edsall, M.D., Professor Emeritus of Microbiology (Harvard School of Public Health and London School of Hygiene and Tropical Medicine).

Theodore C. Eickhoff, M.D., Professor of Medicine, Head, Division of Infectious Diseases, University of Colorado Medical Center, Denver, CO 80262.
(Since July 1, 1976, Professor of Medicine, Head, Division of Infectious Diseases, Vice Chairman,

Department of Medicine, University of Colorado Medical Center, Denver, CO 80262.)

John C. Feeley, Ph.D., Chief, Bacterial Immunology Branch, Center for Disease Control, Atlanta, GA 30333.

Hjordis M. Foy, M.D., Ph.D. Associate Professor, Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195.
(Since July 1, 1976, Professor, Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195.)

Edward A. Mortimer, Jr., M.D., Chairman of the Department of Pediatrics, School of Medicine, University of New Mexico, Albuquerque, NM 87131.
(Since February 1, 1975, Professor and Chairman of the Department of Community Health and Professor of Pediatrics, School of Medicine, Case Western Reserve University, Cleveland, OH 44106.)

Jay P. Sanford, M.D., Professor, Department of Internal Medicine, University of Texas Southwestern Medical School at Dallas, Dallas, TX 75235.
(Since June 1, 1975, Dean, School of Medicine, Uniformed Services University, Bethesda, MD 20014.)

The Panel was first convened on July 12, 1973, in an organizational meeting. Working meetings were held on: July 12, September 24-25, November 9-10, December 13-14, 1973; February 14-15, April 9-10, June 13-14, September 12-13, November 7-8, 1974; January 13-14, February 24-25, May 15-16, June 19-20, September 11-12, November 20-21, 1975; January 12-13, March 27-28, May 17-18, July 22-23, October 23, December 14-15, 1976; March 24-25, December 12-13, 1977 and February 1-2, 1979.

Two nonvoting liaison representatives served on the Panel. Ms. Laryl Lee Delker, nominated by the Consumer Federation of America, served as the consumer representative. John Adams, Ph.D., of the Pharmaceutical Manufacturers Association, nominated by a number of producers with products under review by the Panel, served as the industry representative. Karl Bambach, Ph.D. substituted for Dr. Adams during his absences. Morris Schaeffer, M.D., Ph.D., participated in the panel meetings in his capacity as Director of the Office of Efficacy Review, Bureau of Biologics, Food and Drug Administration. Jack Gertzog, Deputy Director, Office of Efficacy Review, Bureau of Biologics, Food and Drug Administration, served as Executive Secretary of the Panel.

Margaret Pittman, Ph.D. was selected by the Panel as a Consultant.

The following individuals attended one or more of the panel meetings and were given an opportunity to appear before the Panel to express their views regarding the subject of this report or matters relating to it.

John T. Anderson, M.D.

David L. Aronson, M.D.

Michael Alkan, M.D.

Malcom S. Artenstein, M.D.

W. R. Ashford, Ph.D.

Harold Baer, Ph.D.

Ann P. Ball, Ph.D.

Michael Barile, Ph.D.

, F. Barker, M.D.

A. Bawduniak

William B. Beardmore, Ph.D.

R. M. Benzaken

Richard Bogash, Ph.D.

T. J. E. Boksay, M.D., Ph.D.

A. E. Bolyn, Ph.D.

Philip Brachman, M.D.

Dennis Bucerri

Edward Buescher, M.D.

J. Cameron, Ph.D.

Dan C. Cavanaugh, Ph.D.

Sotiros Chaparas, Ph.D.

B. R. Choman, Ph.D.

S. J. Cieciura, Ph.D.

Pinya Cohen, Ph.D.

John A. Collins, M.D.

Lyle Conrad, M.D.

Claire B. Cox

John Craig, M.D., Ph.D.

Ray G. Crispen, Ph.D.

Christiane Delgleize

Michele Deschenes

R. J. Dileo

Bruce Dull, M.D.

Bryon Emery

Jane F. Farber

Roger Feldman, M.D.

John S. Finlayson, Ph.D.

Edward A. Fitzgerald, Ph.D.

Philip J. Forsyth

Marion Fox

Carl E. Frasch, Ph.D.

David W. Fraser, M.D.

George Galasso, Ph.D.

Sam T. Gibson, M.D.

Sam Gilston

Karen Graves

Alan Gray, Ph.D.

Victor Gurewich, M.D.

Erwin Haaf

William H. Habig, Ph.D.

William Hankins, Ph.D.

Carolyn Hardegree, M.D.

L. G. Hershberger, Ph.D.

Bob Herzing

James C. Hill, Ph.D.

Donald Hochstein

Gerd Hoff

Richard Horton, M.D.

Michael Hume, M.D.

Peter Barton Hutt, Esquire

Silvio Landi, Ph.D.

Darrell T. Liu, Ph.D.

J. W. Maloy

Charles R. Manclark, Ph.D.

Elmer Martini

Martha Mattheis

Frank McCarty, Ph.D.

Ann McClenahan

Joseph McCormick, M.D.

Molly McKitterick

I. W. McLeon, M.D.

P. J. McMorrow

D. J. Mehta, M.D.

Harry M. Meyer, Jr., M.D.

John Modlin, M.D.

J. Anthony Morris, Ph.D.

Robert S. Munford, M.D.

A. John Nelson, M.D.

Mark Novitch, M.D.

Joseph P. O'Malley, M.D.

Walter Orenstein, M.D.

A. S. Outschoorn, Ph.D.

Paul D. Parkman, M.D.

Alfred V. Persson, M.D.

Faye Peterson

J. Kris Piper

Margaret Pittman, Ph.D.

Edward L. Platcow, Ph.D.

Suresh C. Rastogi, Ph.D.

Terry Real

Maryann Rench

John B. Robbins, M.D.

John Ropoza

Robert L. Rosenberg, M.D.

B. A. Rubin, Ph.D.

Robert S. Rubin, M.D.

Mario Saletti

Robert A. Sauter, D.V.M.

Alexander Schmidt, M.D.

Rachel Schneerson, M.D.

Alan B. Schulman

Edward Seligmann, Jr., Ph.D.

Sol Sherry, M.D.

Richard T. Silver, Ph.D.

Clay Sisk

James W. Smith, Ph.D.

Lennis Stainer, Ph.D.

Bengt H. Strindberg, M.D.

Scott Swisher, M.D.

Eugene Timm, Ph.D.

E. Tischler

Howard Tint, Ph.D.

R. J. Vallancourt, D.V.M.

Mare Verstraete, M.D., Ph.D.

R. Warrington, Ph.D.

Randolph M. Widmark, M.D., Ph.D.

K. R. Wilcox, M.D.

Robert J. Wilson, M.D.

John Witte, M.D.

A. F. Woodhour, Ph.D.

Alex Young

Sammie R. Young

No persons who so requested was denied an opportunity to appear before the Panel.

The Panel on Review of Bacterial Vaccines and Toxoids evaluated all data submitted for the following vaccines, toxoids and other related products:

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL

| Manufacturer | Product |
|---|---|
| Abbott Laboratories | Tetanus Immune Globulin (Human) |
| Advance Biofactures Corp. | Collagenase |
| Armour Pharmaceutical Company | Tetanus Immune Globulin (Human) |
| Bureau of Laboratories, Michigan Department of Public Health | Anthrax Vaccine Adsorbed |
| | Diphtheria Antitoxin |
| | Diphtheria and Tetanus Toxoids Adsorbed |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed |
| | Diphtheria Toxoid Adsorbed |
| | Pertussis Vaccine |
| | Pertussis Vaccine Adsorbed |
| | Tetanus Immune Globulin (Human) |
| | Tetanus Toxoid Adsorbed |
| | Typhoid Vaccine |
| Connaught Laboratories Ltd. | BCG Vaccine |
| | Botulism Antitoxin |
| | Diphtheria Toxoid |
| | Tetanus Toxoid |

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--con.

| Manufacturer | Product |
|---|---|
| Cutter Laboratories, Inc. | Pertussis Immune Globulin (Human) |
| | Plague Vaccine |
| | Tetanus Immune Globulin (Human) |
| | Tetanus Toxoid |
| Dow Chemical Company (The) | Diphtheria and Tetanus Toxoids Adsorbed |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed |
| | Diphtheria Toxoid |
| | Diphtheria Toxoid and Pertussis Vaccine Adsorbed |
| | Pertussis Vaccine |
| | Tetanus Immune Globulin (Human) |
| | Tetanus Toxoid |
| | Tetanus Toxoid Adsorbed |
| Eli Lilly and Company | Cholera Vaccine |
| | Diphtheria and Tetanus Toxoids |
| | Diphtheria and Tetanus Toxoids Adsorbed |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed |

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--con.

| Manufacturer | Product |
|---|---|
| Eli Lilly and Company--con. | Pertussis Vaccine |
| | Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use) |
| | Tetanus Toxoid |
| | Tetanus Toxoid Adsorbed |
| | Typhoid Vaccine |
| E. R. Squibb and Sons, Inc. | Tetanus Immune Globulin (Human) |
| Glaxo Laboratories, Ltd. | BCG Vaccine |
| Istituto Sieroterapico Vaccinogeno Toscano "Sclavo" | Diphtheria Antitoxin |
| | Diphtheria Toxoid |
| | Diphtheria Toxoid Adsorbed |
| | Tetanus Antitoxin |
| | Tetanus Toxoid |
| | Tetanus Toxoid Adsorbed |
| Lederle Laboratories Division, American Cyanamid Co. | Botulism Antitoxin |
| | Cholera Vaccine |
| | Diphtheria Antitoxin |
| | Diphtheria and Tetanus Toxoids Adsorbed |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed |

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--con.

| Manufacturer | Product |
|---|---|
| Lederle Laboratories Division, American Cyanamid Co.--con. | Gas Gangrene Polyvalent Antitoxin |
| | Pertussis Vaccine |
| | Streptokinase-Streptodornase |
| | Tetanus Antitoxin |
| | Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use) |
| | Tetanus and Gas Gangrene Polyvalent Antitoxin |
| | Tetanus Immune Globulin (Human) |
| | Tetanus Toxoid |
| | Tetanus Toxoid Adsorbed |
| Massachusetts Public Health Biologic Laboratories | Diphtheria and Tetanus Toxoids Adsorbed |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed |
| | Diphtheria Toxoid |
| | Diphtheria Antitoxin |
| | Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use) |

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--con.

| Manufacturer | Product |
|---|---|
| Massachusetts Public Health Biologic Laboratories--con. | Tetanus Antitoxin |
| | Tetanus Immune Globulin (Human) |
| | Tetanus Toxoid |
| | Tetanus Toxoid Adsorbed |
| | Typhoid Vaccine |
| Merck Sharp & Dohme, Division of Merck & Co., Inc. | Cholera Vaccine |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed |
| | Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use) |
| | Tetanus Toxoid |
| | Tetanus Toxoid Adsorbed |
| | Tetanus Immune Globulin (Human) |
| | Typhoid Vaccine |
| Merrell-National Laboratories, Division of Richardson-Merrell Inc. | Cholera Vaccine |
| | Diphtheria Antitoxin |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine |

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--con.

| Manufacturer | Product |
|---|---|
| Merrell-National Laboratories, Division of Richardson-Merrell Inc.--con. | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed |
| | Diphtheria Toxoid |
| | Pertussis Vaccine |
| | Tetanus Antitoxin |
| | Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use) |
| | Tetanus Toxoid |
| | Tetanus Toxoid Adsorbed |
| Metabolic, Inc. | Tetanus Immune Globulin (Human) |
| Osterreichisches Institut Fur Haemoderivate G.m.b.H. | Tetanus Immune Globulin (Human) |
| Parke, Davis and Co. | Diphtheria and Tetanus Toxoids |
| | Diphtheria and Tetanus Toxoids Adsorbed |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Poliomyelitis Vaccine |
| | Diphtheria and Tetanus Toxoids and Pertussis and Poliomyelitis Vaccines Adsorbed |

TABLE 1--LIST OF PRODUCTS REIEWED BY PANEL--con.

| Manufacturer | Product |
|---|---|
| Parke, Davis and Co.--con. | Diphtheria and Tetanus Toxoids and Pertussis Vaccine |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed |
| | Diphtheria Toxoid |
| | Diphtheria Toxoid Adsorbed |
| | Pertussis Vaccine |
| | Pertussis Vaccine Adsorbed |
| | Tetanus Antitoxin |
| | Tetanus Immune Globulin (Human) |
| | Tetanus Toxoid |
| | Tetanus Toxoid Adsorbed |
| Swiss Serum and Vaccine Institute Berne | Tetanus Antitoxin |
| | Tetanus Toxoid Adsorbed |
| Texas Department of Health Resources | Diphtheria and Tetanus Toxoids Adsorbed |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed |

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--con.

| Manufacturer | Product |
|---|---|
| Texas Department of Health Resources--con. | Diphtheria Toxoid |
| | Pertussis Vaccine |
| | Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use) |
| | Tetanus Toxoid |
| | Typhoid Vaccine |
| Travenol Laboratories, Inc., Hyland Division | Pertussis Immune Globulin (Human) |
| | Tetanus Immune Globulin (Human) |
| University of Illinois | BCG Vaccine |
| Wyeth Laboratories, Inc. | Cholera Vaccine |
| | Diphtheria and Tetanus Toxoids Adsorbed |
| | Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed |
| | Diphtheria Toxoid |
| | Diphtheria Toxoid Adsorbed |
| | Pertussis Vaccine |
| | Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use) |
| | Tetanus Immune Globulin (Human) |

PANEL ON REVIEW OF BACTERIAL

VACCINES AND TOXOIDS

August, 1979

The Advisory Panel appointed to review data and information concerning safety, effectiveness, and labeling of Bacterial Vaccines and toxoids has completed their review as follows:

BASIS OF EVALUATION

1. General background and history. The diseases of man caused by bacteria and by some of their specific extracellular toxins from which useful vaccines have been produced represent extraordinarily diverse pathologic processes. The diseases range from tetanus to tuberculosis; the former is an acute illness caused by a single well-defined toxin and the latter is a chronic disease due to intricate bacterial-host cell interactions resulting in a wide variety of lesions. Moreover, the degree of protection offered by current immunization practices against these diseases range from virtually complete efficacy, as in the case of tetanus, to a very limited and temporary benefit, as in the case of cholera. A brief account of the history of immunization against these diseases may help both the lay and professional public to appreciate the background of our current achievements and dilemmas against which this Panel has been obliged to exercise its judgment in assessing the safety and efficacy of the products under its purview.

It is important for the public and its agencies to appreciate the tentative and evolving nature of the science of immunization, particularly to combat the notion that decisions made in the public interest at one point in time are necessarily valid and binding at another. The foundations of the modern science of bacteriology are no more than a century old and were laid by Louis Pasteur and Robert Koch, who died within the memory of some persons still alive. Pasteur not only established the germ theory of disease, but, just one hundred years ago (in 1877) he discovered and applied the principles of active immunization by using living, attenuated cultures--"live vaccines." He argued that if Jenner could use cowpox (what Pasteur thought to be attenuated smallpox) as a vaccine, the same might be done with attenuated anthrax. This he succeeded in doing in preparing attenuated chicken cholera and anthrax vaccines for animals. Subsequently, "killed" bacterial vaccines were made by the end of the 19th century when A. E. Wright in England, among others, began immunizing against typhoid fever with heat-killed whole bacterial cells. Epidemics of cholera and plague, rampant in various parts of the world at that time, were quickly attacked with other vaccines many of which were similarly made from killed whole bacteria. In all three diseases, the vaccines seemed to afford some useful protection before advances could be made in worldwide sanitation and well before the introduction of antibiotics.

At the close of the 19th century, Koch was attempting to prevent and even to treat tuberculosis with tuberculin, the culture filtrate of tubercule bacilli. His failure to do so, plus the serious toxic and

untoward effects that this treatment had on the disease, created reservations in the minds of both professional and the public concerning the risks as well as the benefits of immunization attempts. Nonetheless, despite this setback, the first living bacterial vaccine to be used on a large scale in man came as a sequel to Koch's work when Calmette and Guerin introduced BCG vaccine into human immunization procedures in 1921.

To appreciate the speed of the development of the science of immunology, it is necessary to acknowledge not only the dramatic empirical discoveries of successful vaccines, but also the discovery of the immunologic processes upon which further progress in immunization was based. Two major forms of host defenses are referred to repeatedly in this report. They also have their origins in the medically tumultuous era of the late 19th century. Eli Metchnikoff, the Russian biologist who studied under Pasteur and eventually became a director of the Pasteur Institute, developed the concept of "phagocytosis." He gave the name of "phagocytes" (eating cells) to body cells in blood, blood vessels, lymph nodes, bone marrow, liver and spleen which digest and destroy invading microorganisms as well as other foreign microparticles. This system of cellular immunity, responsible for the clearing of foreign agents from within the host, he considered to be the backbone of host defense against infection. The "humoral theory" was introduced at the same time by G. H. F. Nutthall of Cambridge who studied the killing action of blood on bacteria (bactericidal effects). He showed these effects were due to chemical products of cells in blood serum and body fluids; substances called "antibodies" which could destroy or inactivate

some bacteria without help from phagocytes. By 1894, Richard Pfeiffer, one of Koch's pupils, demonstrated that such antibodies caused the disintegration of cholera vibrios. These he called "bacteriolysins."

The synthesis of humoral and cellular mechanisms of immunity was proposed by Wright in 1903 when he demonstrated the pro-phagocytic effect of specific antibodies. Wright named antibodies "opsonins" or "bacteriotropins" which enhance the ability of phagocytic cells to recognize, ingest and kill microorganisms. Although Wright's concepts of the interaction of antibodies and cells applied well to antibacterial immunity against invasive bacterial diseases such as typhoid, pneumonia, streptococcal infections and meningitis, it did not pertain as much to diseases produced by the action of toxins liberated by bacteria.

In diseases like diphtheria, tetanus and botulism, neutralization of the soluble bacterial toxins (exotoxins) liberated during infection is of the utmost importance in the prevention of the diseases caused by these organisms. Thus, antibodies which neutralize such toxins are the basis of "antitoxic immunity" which constitutes an area of immunologic knowledge that is on a much firmer basis than the understanding of many forms of antibacterial immunity.

Again, in the last two decades of the 19th century, the principles of antitoxic immunity were established when Pasteur's associate, Pierre Roux, showed that the diphtheria bacillus produced a powerful soluble toxin in the culture filtrate of the organism. Behring and Kitasato,

disciples of Koch, by 1890 had prepared an antibody to the diphtheria toxin which they termed "antitoxin" and with such immune sera began the era of "passive immunization." Thus, antitoxin (serum prepared in horses against such toxins) could be used to prevent and treat certain diseases. The denaturation of the toxins with the addition of formalin rendered them harmless when injected into man and animals but they still retained their ability to produce antitoxin antibodies. "Active" immunization against diphtheria and tetanus with these toxoids subsequently became routine in most countries of the world.

"Passive" immunization consists of the injection of antibodies made by another host, human or animal, into the person to be protected. Antibodies remain in that person for only a short time, however, until they are broken down, and thus provide only temporary benefit. Active immunization, on the other hand, consists of inducing the person to be protected to produce their own antibodies by giving small doses of the microorganism or toxin in a form that will not cause serious illness in the person. Once active immunity is induced, it tends to persist for long periods of time.

The important differences between passive and active immunization were clearly established in the 1890's by Jules Bordet and by Paul Ehrlich whose brilliant career not only included the standardization of toxins and antitoxins and the foundations of modern immunochemistry, but also led to the recognition of the presence in the blood and body tissues of "complement," the system of enzymes which are activated by antigen-antibody complexes and which result in the cellular and vascular events

of inflammation leading to the destruction of bacteria and viruses and to the stimulation of the host cells which phagocytize and destroy organisms.

From Ehrlich's systematic, quantitative approach to the neutralization of toxins emerged the triumph over diphtheria and subsequently, even more brilliantly, over tetanus. By the First World War, the lives of many wounded men were saved by passive tetanus immunization and the control of tetanus during the Second World War with the toxoid could be regarded as a modern miracle of immunization.

Soon after the beginnings of immunology, came the development of government supervising authorities in many countries, to regulate standards of purity and potency to which preparations had to conform before they were released for public usage. The importance of international standards for vaccines was recognized by the Health Commission of the League of Nations which in 1929 appointed a permanent Commission on Biological Standardization. As a result, potency of vaccines were expressed in a more uniform notation which was accepted and understood throughout the world.

In the United States and Great Britain, the control of biological substances, for sale, became essentially the responsibility of the producing laboratory, but manufacturers worked under licenses issued by government agencies such as the current Bureau of Biologics, Food and Drug Administration and Great Britain's Ministry of Health, respectively, and under standards of safety and potency defined by the regulations developed by these agencies.

It has become generally understood that a successful and acceptable vaccine must be: (1) safe and (2) effective. Safety means that the preparation used must not cause the disease against which it is directed and that the occurrence of reactions, both local and general, must be within acceptable limits. Efficacy implies a useful degree of clinical protection: in some infections, the best guide to immunity is the amount of circulating antibody in the blood against the causative agent. It is the clinical trial, however, which must provide the final critical assessment of the efficacy and safety of the new vaccine. The basic requirements of field trials meeting modern critical criteria were well described by 1957 by W. C. Cockburn, and are elaborated upon in the Panel's generic statement on the requirements for a well-controlled field trial.

The World Health Organization, which was established in 1948, encouraged international cooperation in solving health problems and has been helpful in continuing with the work on establishing and promoting international standards for biological products which had begun with the work of the League of Nations.

The growing sophistication of the standardization of vaccines ultimately resulted in changes in Federal law and regulations whereby this Panel was established to help to determine whether currently licensed vaccines produced according to specified standards of potency are both safe and effective for human usage. Although the aims of the act are praiseworthy and the action timely, the judgment concerning safety and

efficacy of bacterial vaccines and toxoids presents some complex and knotty overall problems.

2. Overall problems--a. Determination of safety--(1) Risk/benefit assessment. The concept of risks and benefits is a fundamental one in a consideration of vaccines, or any other therapeutic or preventive modality. Risks are considered to include the risk of an adverse reaction to the vaccine; benefits, however, include not only the likelihood that a vaccine will protect against a disease, that is, its efficacy, but also that it will ameliorate the severity of the disease to be prevented. Greater risks of adverse effects might be tolerated for a vaccine that provided protection against a lethal disease than for a vaccine against a disease that is basically benign. Furthermore, "benefit" may extend not only to the recipient of the vaccine, but in some cases to society at large.

The risks versus the benefits of the vaccines covered in this report are, like other features of these vaccines, very diverse. Standards of safety must again be individualized for each kind of vaccine. For example, tetanus toxoid is among the safest of all vaccines and its benefits are enormous. Attempts to further reduce its reactivity must not therefore, jeopardize its efficacy. Although the benefits of pertussis vaccine in infants have occasionally been questioned, the preponderance of expert judgment is definitely favorable. But this vaccine is highly reactive and very justifiable attempts to reduce its reactivity by purification are virtually thwarted by the dependence of the assessment of efficacy upon a mouse protection model which must be linked to

clinical trials to confirm its validity. Despite the vaccine's hazards, therefore, attempts to modify it to improve its tolerance are difficult with present knowledge.

Risk/benefit assessments vary not only between one generic group of vaccines and another, but within a generic category, each product must be assessed individually for its special features that vary from the norm. In addition, some products were modified without updated evidence of their clinical efficacy. In some very uniform vaccines, such as tetanus toxoid, a relatively minor change in production to achieve greater purification or a decreased concentration of toxoid to reduce reaction rates, was examined by the Panel very critically because of the need to ensure that the vaccine performed at its expected high level of protection.

The concept of risk/benefit also includes the public's as well as the individual's protection. A vaccine that produces considerable discomfort and sometimes even severe general reactions is more acceptable if the protection it affords the individual also results in protection of the community by reducing contagion. Such is the case in vaccination against pertussis, a contagious disease particularly dangerous to very young infants but dramatically controlled by a rather reactogeni vaccine. In contrast, cholera vaccine exerts little or no effect on the prevalence or spread of the disease and acceptance of its reactions is limited.

(2) Adjuvants. In the course of its deliberations, the Panel was informed by the Bureau of Biologics of the results of studies of the

effect of injection of aluminum adjuvants into special strains of white mice which have a very high natural incidence of fibrosarcoma of the skin. Such mice have been used in some screening studies for the oncogenicity of certain drugs. The experiments showed some enhancement in the rate of formation of fibrosarcomas in the mice that received aluminum adjuvants. The Panel asked for expert interpretation of the design and results of the mouse studies by scientists from the National Cancer Institute and Roswell Park Memorial Institute. These consultants concurred with the Panel in their opinion that the mouse findings were indeed reliable for the design of the experiments but that the significance of the findings for man could not be assessed from this model alone and that studies in other mammalian species should be made.

The Panel therefore surveyed data in man on fibrosarcomas in different populations from various cancer registries. These show that fibrosarcoma is a rare tumor, the incidence increasing sharply in old age. Cohorts were analyzed who were probably exposed to aluminum adjuvants, such as males born around 1920 who probably received immunizations during World War II whereas the women generally did not. No increased rate of sarcoma in males in that cohort was detected. Because most Canadian vaccines do not contain aluminum adjuvants, mortality rates in Canada were compared with those in the United States for fibrosarcomas. Rates of connective tissue tumors were slightly higher among United States than Canadian males, but the rates for females were similar. The data did not disclose any major differences that would cause concern

over the use of aluminum adjuvants whose benefits are considered to be of major value in the primary immunization of children with DTP vaccines. The Panel encouraged further studies on adjuvants, especially retrospective studies in humans, but did not consider that their recommendations for the safety and efficacy of DTP vaccines containing aluminum adjuvants should be modified at this time.

(3) Liability and legal problems. Almost any clinical investigation to improve well established and highly beneficial vaccines, or to assess more accurately their current reaction rates, is frustrated by the threat of malpractice suits and claims for damages against manufacturers. Physicians who administer vaccines as well as those who produce them feel threatened when reporting adverse reactions, even when the vaccine has been prepared and used in accordance with government regulations and recommendations. Moreover, some reactions are intrinsic to the process of human immunization and range from psychic trauma to fatal idiosyncratic reactions that are extremely rare and are an unavoidable hazard of introducing foreign substances into humans.

The United States has been backward in its failure to deal with the risks and responsibilities of immunization. Several European countries and Japan have established a public compensation system under which their governments have accepted responsibility for the recognized hazards of immunization. Some of these laws provide for compensation from public funds to patients suffering damage from vaccinations that are recommended by competent authorities. Damages have been paid as pensions.

The differences between the primary responsibility of the manufacturer and the ultimate responsibility of the state should be distinguished. The former should comply with the regulations of production and marketing procedures. If these obligations are fulfilled and the vaccine is administered correctly, responsibility for immunization accidents should rest with the official agencies recommending them. Unlike many other countries, the United States has not dealt adequately with this issue of immunization, and attempts to further improve vaccines will be hampered. Furthermore, collection of data to establish the efficacy of some of the current licensed products may also be hampered by this deficiency of public policy in the United States.

b. Determination of efficacy--(1) The diverse immunologic actions of the vaccines. The various vaccines which have been lumped together for this Panel's review are so diverse that standards of efficacy which apply to one may not apply to another at all. Progress in immunology is far greater in areas relevant to the effects of some vaccines compared to others. For diseases in which immunity depends upon specific antibodies which either neutralize toxin or which opsonize bacteria and lead to their prompt destruction within phagocytes, induction of such antibodies correlates well with protection and the measurement of such antibodies may reflect efficacy quite faithfully.

In many other kinds of antibacterial immunity, however, survival of organisms within cells after ingestion is a particular feature of the host-parasite contest. In these infections the role of cellular immunity

is critical. Diseases such as tuberculosis and typhoid fever are illustrative of infections which may be considered intracellular as well as extracellular. Our knowledge of immunity in such diseases still awaits greater understanding of the cell-mediated defense process. The effects of vaccination therefore remain empirical in these diseases and can be established at present by field trials alone. In pertussis, for example, the relative roles of humoral and cellular immunity are not at all clear and the antibodies that can be measured may or may not be protective.

Finally, protection against a disease such as cholera has been proven in recent studies, to depend primarily upon the prevention of the attachment of the cholera vibrios to the surface of intestinal epithelial cells. The solution of this problem appears more feasible than the more complex antibacterial immunity of diseases like typhoid fever.

(2) Establishing standards of efficacy. It should be apparent that a standard of efficacy must be applied separately to each vaccine according to current expectations of its performance. For example, for the prevention of tetanus an almost perfect performance can be expected. Moreover, its efficacy can be quite accurately assessed by serum antitoxin levels. For diphtheria, the standard of efficacy is also high, but there is less certainty as to what level of antitoxic immunity constitutes adequate protection because strains of diphtheria may vary greatly in the amount of toxin they can produce and absolute immunity based on a given level of antibody is less predictable.

A major dilemma repeatedly faced by the Panel was the decision as to whether to place a given product in Category I or Category IIIA. The law requires that each product be proven to be both safe and effective in man; for many products, licensed prior to the current, more stringent legislation, specific data related to efficacy are not available. Even in the absence of such data, however, the Panel has little doubt that the efficacy of tetanus and diphtheria toxoids are satisfactory because it is reasonable to infer that if they were not satisfactory, the remarkable reductions in tetanus and diphtheria associated with widespread use of these vaccines surely would not have occurred. Moreover, the techniques of production suggest that they should be efficacious.

But the charge to the Panel was to examine each licensed product from the standpoint of the scientific evidence that each is both safe and effective in humans. The various toxoids placed in Category IIIA by the Panel are believed to be entirely acceptable in terms of safety. The Panel believes that many are effective, but, in the absence of recently obtained proof in humans for certain specific products, the Panel's charge to affirm the effectiveness of individual products, could not allow a Category I assignment.

The feasibility of obtaining efficacy data is technically simple in the case of the toxoid vaccines (tetanus and diphtheria) because serum neutralizing antibodies are readily measurable and these reflect efficacy accurately. Blood samples from relatively small numbers of healthy volunteers (s prototype model for study with 20-40 individuals) who receive immunization

can therefore establish efficacy. Obtaining blood samples from healthy volunteers receiving licensed vaccines, particularly children and infants, is a problem currently complicated by recent regulations on informed consent. However, the difficulties which may be perceived in obtaining such data do not outweigh the importance to the public of assuring the efficacy of these universally administered vaccines in achieving primary immunization. For these reasons, the Panel recommends that products, for which the human data requested are not available, be assigned to Category IIIA.

In the case of pertussis, the situation is peculiar. Though the vaccine is a very effective one, it is quite crude, consisting either of killed whole cells or of a soluble product of the organism. The nature of immunity is unknown. The disease has almost disappeared in the United States, making field trials, at least in this country, impossible. The standard of efficacy is tied to a highly artificial mouse model of protection--one that bears essentially little similarity to the natural disease in man. Yet the last successful field trials conducted decades ago are tied to current products whose toxicity represents the major concern about the vaccine. Any move to make the vaccine safer by modifying it is fraught with the danger of altered efficacy which cannot be adequately assessed without an extensive field trial.

The plague and cholera vaccines place the Panel in the apparently inconsistent position of classifying them as effective without the extensive efficacy data which are available for other vaccines. These

vaccines are of decidedly limited value. At the same time, the Panel demands of tetanus updated data on antibody levels when relatively small changes in the vaccines have been introduced recently into the manufacturing process. The expectations of efficacy from the current plague and cholera vaccines are obviously quite different than those expected from tetanus.

Finally, standards for judging efficacy of currently available BCG vaccines are far from satisfactory. No reliable animal model or immunologic test has yet been discovered which accurately reflects human immunity; nobody can prove that the live vaccine strains have remained unchanged by repeated passage in the laboratories where they are maintained; and only new field trials that are in progress but are several years from completion can determine efficacy. Even then such efficacy would have to be related only to the strains used in the trial. Nonetheless, decisions have to be made based on past performances and to some degree upon the assumption that the strains of current vaccines are retaining their immunizing power. Lacking other alternatives, the decision for efficacy was made by the Panel with full knowledge of the assumptions that were made.

(3) Extrapolation of data from the use of combined vaccines. Practical considerations in the evaluation of efficacy for some products when data were unavailable, made it desirable and sometimes necessary to extrapolate from data on the use of combined vaccines. This approach

appears to be logical and valid, particularly for diphtheria, tetanus, and pertussis vaccines, because of the wide use of the combined diphtheria, tetanus, and pertussis vaccines and the endorsement of this immunization practice by all leading biomedical experts in this country. Accordingly, the Panel made use of the following extrapolation models whenever it seemed appropriate because of the availability of data:

1. Diphtheria tetanus and pertussis (DTP) could provide efficacy data for pertussis (P) (but not for diphtheria (D) and tetanus (T) due to adjuvant effect of pertussis).

2. Tetanus and diphtheria (Td) could provide efficacy data for T and also possibly for diphtheria and tetanus (DT) and D if the small 2 Lf dose of DT in Td proved adequate. Caution would be necessary in extrapolating Td data in adults to children 6 years of age or younger.

3. DT could provide efficacy data for D, T and for the T component of Td.

| Combined Product Available | Would Provide Efficacy Data for: |
|---|---|
| DTP | P |
| Td | DT* D* T |
| DT | D T Td (T-only) |

*If response of 2 Lf Diphtheria toxoid were satisfactory, the larger amount in "D" products could be assumed satisfactory.

(4) Patient participation, informed consent and clinical trials. When sufficient data were not available from which to determine efficacy, the Panel had to consider the feasibility and cost benefit of the required further clinical investigation. Such factors stimulating the Panel's desire for more data were: (i) changes in the manufacturing process, the concentration of antigen, the purification of the product, or the additions of preservatives or adjuvants; (ii) the dependence of some manufacturers upon clinical data establishing the effectiveness of the same vaccine made by others; (iii) possible changes in the state of immunity of the population and secular changes in the epidemiology of the disease; (iv) the need for better products or immunization schedules to increase efficacy or decrease reactivity.

On the other hand, the Panel was mindful of the growing difficulties of obtaining participants and informed consent for clinical trials--even those as simple as obtaining a few samples of blood per patient by venipuncture. For primary immunization trials, the need to obtain consenting subjects who have no prior immunity imposes a further stringent limitation. If clinical trials were to require more than an assessment of humoral responses, the inability to evaluate protection against a challenge of natural disease in this country (such as in the case of tuberculosis or pertussis) made insistence upon such data unreasonable. The dilemmas of inadequate clinical data to judge efficacy versus limited access to such data, led to productive discussions and workshops with manufacturers and the Bureau of Biologics to establish efficient

and relatively standard protocols which would supply the required data from minimal numbers of participants and at minimal costs. The Panel's general recommendations contain suggestions arising from these conferences.

(5) Animal models. Animal models of the human diseases in which vaccines may be accurately and reliably assayed for safety and efficacy would solve many problems of clinical investigation and human trials. The Panel found this need particularly cogent in the case of pertussis and tuberculosis in which animal models were inadequate and field trials not feasible. In these instances recommendations that vaccines be classified in Category IIIA to obtain further proof of safety and efficacy will be greatly handicapped unless animal models are developed which correspond closely to the human disease counterpart.

(6) Administrative problems. Several administrative problems had to be solved by the Panel to carry out its charge and mission. Some licenses had been held on products which the manufacturers had not marketed for many years. Some of these products were intended to be used only when the vaccine was combined with others (for example, monovalent diphtheria toxoids). Some antiserums (equine diphtheria antiserum) and some toxins (diphtheria toxin for Schick testing) were considered useful for limited purposes only. They might be in limited supply, therefore, unless publicly subsidized. During the course of the Panel's review, licensed products were updated because of modifications, and license applications were amended to replace outdated products (for example, plague vaccine).

(7) Related issues. Careful attention was given to the opinions and policies of other governmental agencies and professional societies concerning the safety, efficacy and recommended usage of the vaccines reviewed. The Panel was mindful that its decisions were concerned primarily with assessing evidence of safety and efficacy of the vaccines rather than determining either public health or clinical practice policy governing their usage. It was gratifying, however, that very few significant differences of opinion were encountered among recognized authorities. The most divergent opinions related to the issue of the efficacy of the BCG vaccines and reflected the need to establish whether or not prolonged storage and passage of the seed strains in laboratories had led to changes in their efficacy. Limited enthusiasm for the use of BCG by public health authorities in the United States as a means for the control of tuberculosis had to be weighed against: (i) evidence of efficacy; (ii) alternative strategies for control; and (iii) the right of manufacturers to produce and physicians to use a vaccine, if effective, in some parts of the world and in some populations of the United States with unusual risks of exposure to tuberculosis. Although some would have preferred a "Category III" classification for BCG, requiring updated clinical data of efficacy, the feasibility of obtaining such data in the ensuing several years appeared remote and unnecessary at this time when weighed against the favorable evidence for BCG. The Panel was faced with having to make an "effective" versus "ineffective" judgment on the basis of the evidence at hand and the evidence, although incomplete, clearly called for a judgment of effectiveness.

3. General recommendations--a. Support for widespread immunization programs. Universal active immunization for the prevention of tetanus, diphtheria, and pertussis should be accomplished to take full advantage of the great effectiveness of these vaccines and to obviate the inherent risks, cost and effort of passive immunization which is incompletely effective in the first two diseases and not effective in the third.

b. Liability legislation for immunization. Assessment of the safety of vaccines requires improved procedures for reporting adverse reactions. This in turn requires the development of a more enlightened public policy which includes acceptance by the United States Government of responsibility for the recognized and unavoidable hazards of immunization.

Legislation is urged that will provide compensation from public funds to individuals suffering damage from vaccinations that are recommended by competent authorities, carried out with vaccines that passed official safety and efficacy review, and that were administered by recommended techniques. Such legislation will not only greatly improve assessment of safety but will also enhance collection of the data necessary to establish efficacy by reducing the professional liability issues in clinical investigation of vaccines.

c. Improved efficacy of clinical investigation. The Bureau of Biologics should offer guidance to manufacturers with regard to recommended protocols which would help to provide adequate clinical data for

assessing vaccine efficacy. Because of the increasing difficulties in obtaining informed consent to conduct studies on normal individuals, even studies requiring no more than serial venipunctures, it would be most efficient and economical to develop protocols which would provide required information with the fewest numbers of participants and specimens. These considerations are especially appropriate in studies involving children. Cooperation among manufacturers and the Bureau of Biologics should be promoted to adopt relatively standardized protocols that might set minimum limits to the numbers of individuals required to achieve statistical strength of data and appropriately controlled conditions, laboratory methods, and population groups.

Currently there is a conflict between the public's need for precise data regarding the safety and efficacy of immunization programs and the rights of the individual, both in terms of experimental risk and privacy. Despite the need to protect the privacy of the individual, a mechanism should be developed that would provide means of access for authorized investigators to demographic and health data on individuals in order to conduct long-term follow-up studies of immunization procedures.

d. Improved production procedures. Some standards of purity, immunogenicity and immune responses for well established vaccines are based upon old-fashioned methods which should be updated by more sophisticated techniques made possible by advancing scientific knowledge. Efficacy and safety should be assessed and defined in terms of more

modern standards of quantitative immunobiologic testing, chemical purification and clinical evaluation. The motivation and impetus to accomplish this is unlikely to come spontaneously from pharmaceutical manufacturers unless review of vaccine licensure is conducted periodically. In addition, workshops should be promoted regularly by the Bureau of Biologics to encourage progress in methodology and to coordinate further efforts at standardization.

e. Research priorities--(1) Animal models. There is great need to develop animal models which accurately predict vaccine responses in man. Throughout the Panel's review, one of the most frequently recurring problems was the need to minimize our dependence on the laborious, collection of expensive and often virtually unobtainable clinical data in order to determine efficacy. Manufacturers are not primarily responsible to implement the quest for animal models and the development of such models will require public research support.

(2) Laboratory tests and procedures. Increased emphasis is needed on the development of laboratory tests and procedures which reflect vaccine efficacy with sufficient accuracy so as to minimize the need for field trials. Improved immunologic tests, the use of tissue culture assays, and relatively simple, reliable and low risk clinical procedures, such as skin tests, would simplify clinical investigation of vaccine efficacy.

(3) Collaborative and cooperative studies. These should be encouraged particularly when such group efforts at collecting data may reduce

the cost and effort and increase the availability of opportunities for clinical investigation, or may resolve quickly and efficiently such issues as dose schedules and the frequency and intervals of injections of vaccines within a generic group which are comparable in potency.

(4) Areas of limited knowledge concerning effective vaccines. Support is needed for research in areas where knowledge of the mechanisms of immunity is limited. It is possible that the judgment of a vaccine as safe and effective may actually discourage research by lowering the apparent priority for the need to improve the vaccine. In diseases such as pertussis, typhoid fever and tuberculosis, the mechanisms by which immunity is produced and the specific antigens which are responsible for the induction of immunity and for reactogenicity, are poorly understood. Further research efforts to reduce the toxicity of these vaccines and to improve their effectiveness will require specific public support.

(5) Increased efficiency of effective vaccines. Support should be available for clinical investigation in areas of vaccine research where it is likely that further progress can be made even where a high degree of vaccine efficacy already exists. An example would be the improvement of the already very safe and effective tetanus vaccines by reducing the number of injections required to achieve primary immunization.

(6) Unmet needs. Finally, research is needed to fulfill unmet needs in protection against bacterial infections. Streptococcal, staphylococcal, gonococcal, hemophilus and pseudomonas infections, to name but

a few, are potentially preventable by immunization. Moreover, there are some products that are needed and can probably be prepared but are not available now, such as botulinus human immune globulin and diphtheria human immune globulin.

f. Assurance of vaccine availability. Close surveillance is necessary of certain vaccine products whose ongoing production in the United States may be discontinued or suspended for commercial reasons despite current or potential needs. Diphtheria toxin for Schick testing and equine diphtheria antitoxin for the treatment and passive immunization of diphtheria are two examples. Continued interaction between the Bureau of Biologics and the Center for Disease Control should be encouraged to ensure government stock piling of required products that are no longer produced commercially.

In addition, some products are produced solely by foreign firms. The Istituto Sieroterapico Vaccinogeno Toscano Sclavo pharmaceutical firm in Italy is a major source of diphtheria antitoxin and the status of diphtheria antitoxin produced in the United States is uncertain. Connaught Laboratories of Canada is the only producer of trivalent botulinus antitoxin. Furthermore, a major vaccine produced by a single domestic firm represents an inherent danger, in that the public is dependent upon a limited source without well defined mechanisms for the control of production and supply.

Public policy needs to be formulated more thoroughly in the entire area of production and supply of vaccines. Prospective planning and

negotiation between public agencies and the pharmaceutical industry should be established as a process by which to ensure vaccine availability when the market alone is inadequate to accomplish this end. Consideration should be given to the establishment of a National Vaccine Commission which can address itself to the solution of these problems.

g. Improved reporting of adverse reactions. At present, there are virtually no standards set for what constitutes untoward reactions to vaccines except their most severe and dire complications; therefore it is difficult to document the actual reactogenicity of some products. Standards for "threshold reactions" above which reports are required need to be established for each generic group of vaccines. The Study Commission on Drug Use which is studying adverse drug reactions should be urged to consider reactions to biological products as well.

h. Improved labeling. Review of the labeling of products submitted to the Panel identified a number of deficient areas in which substantial improvement should be made. A standard for adequate labeling along the lines outlined by the generic labeling statement of the Panel should be adopted so that the accuracy and readability of all labeling can be brought to an optimally useful level.

i. Improved administrative procedures--(1) Periodic review of all licensed vaccines. Periodic review of all licensed vaccines should be carried out to assure that the safety and efficacy of these products are kept current and that standards of production and assay are modernized.

(2) Limited term for vaccine licenses. By limiting the period for which vaccines may be licensed, all products, old and new, will be assured regular review. Furthermore, new vaccines which have only limited evidence of efficacy or for which the clinical efficacy data need to be extended by further experience (situations in which we now assign the "category 3A," i.e., insufficient data but probably effective) should be provisionally licensed for only limited periods of time within which additional data can be generated.

(3) Revocation of licenses for nonmarketed vaccines. Some products which have not been marketed for many years are still licensed and it is not known whether they would still qualify as safe and effective products if and when production is resumed. Some products have never been marketed in the form for which licensed. In the light of current efficacy review standards, it would be better policy to revoke such licenses and require reapplication when necessary.

(4) Consistency of efficacy data. Protocols for efficacy studies should be reasonably consistent throughout the industry for any generic product and should employ standard tests, standard procedures for conducting tests, and standard reference sera. It would be advantageous to develop industry-wide, consistent, standardized guidelines for adducing required data. Such standardized procedures may need review and updating periodically, as new improved laboratory tests become available.

j. International cooperation. The Panel recommends that international coordination of vaccine standardization and assessment of

safety and efficacy be encouraged through groups such as the World Health Organization, the International Association for Biological Standardization and between ministries of health of various countries. In many instances the assessment of vaccine efficacy may be possible only in those countries where an opportunity for field trials may exist.

k. Role of review panels. Judging from the experience of the Panels during their reviews, their current roles as advisory groups should be extended so that they may continue to serve to help assess future safety and efficacy issues that arise with new or improved vaccines.

l. Privacy of panel sessions. The Panel has had little problem in performing its functions at open sessions and believes that closed sessions are necessary only to protect the rights of confidentiality to which license submissions are entitled. The Panel also has had no objection to having its sessions taped and recorded.

m. Transcription policy. The cost/benefit of verbatim transcription of the entire deliberations of the Panel especially those that lead to a documented report is, however, very limited. Verbatim transcription of the vast amount of tedious and noncontroversial detail covered in reviews is enormously wasteful, inhibits free, relaxed and creative discussion and exposes panel members to the risk of remarks and opinions which may be only tentative and which may be quoted out of context.

4. Summary of unresolved problems. In concluding its report, the Panel deems it important to call attention to some of the major unresolved problems which have made its advice and decisions most difficult

and which will continue to hamper the assessment and the improvement of the safety and efficacy of vaccines.

a. Emphasis upon proof of efficacy and upon critical standards of the scientific quality of vaccine data may inhibit the motivation to modify and improve current vaccines and to introduce new ones. If rigid and critical standards are to be set and met, much effort should be put into finding efficient and effective ways to encourage and expedite the conduct of such research.

b. The complexity of the legal and administrative procedures deemed necessary to ensure the protection of the rights of individuals participating in clinical investigations impose serious restraints to the acquisition of vaccine efficacy data since such studies are usually undertaken in normal individuals and often, in the case of universally administered vaccines, in relatively low risk groups. Public policy will have to be formulated to provide incentives to both clinical investigators and participants to engage in the carefully designed field trials and other controlled experiments that are now required. The United States public should share as a whole in the responsibility to participate in such studies. As previously noted in section 2.b. (2) of this introduction, the difficulties which may be perceived in obtaining such data do not outweigh the importance to the public of assuring the efficacy of these universally administered vaccines in achieving primary immunization.

c. Standards of efficacy will have to be evolved for products that are not amenable to clinical trial (e.g., botulism antitoxin).

d. Emphasis upon the individuals' rights of privacy of personal health data can conflict with the public's need for data on immunizations which requires access to health records. Specific exceptions will have to be written to the laws protecting confidentiality of public health information which is now regarded as private.

e. Finally, the glaring absence of a coordinated national immunization policy that would efficiently implement and expedite vaccination procedure and vaccine development, production and supply is now apparent. Such a policy should be formulated without further delay so that future decisions on vaccine safety and efficacy can be made with greater assurance of public acceptability and support.

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## LABELING

Review of the labeling of products submitted to the Panel on Bacterial Vaccines and Toxoids identified a number of deficient areas in which, in the judgment of the Panel, substantial improvement should be made. The following generic comments on the subject of labeling highlight the view of the Panel on what constitutes adequate labeling, and provides a standard such that all labeling can be brought to an optimal level.

### General Comments

Labeling should meet the following general criteria:

The labeling should be written in clear English. In many instances, current labeling is written with very complex sentence structure. There is very often marked ambiguity of meaning. In some instances, even panel members charged with reviewing the subject were unable to determine the precise meaning of statements in the package insert; the physician who may be expected to give the labeling little more than a cursory reading therefore may often receive inadequate guidance.

The labeling should be easily legible, and printed in such a fashion as to attract, rather than to repel or discourage the reader. Much of the present labeling is printed in type so small as to discourage all but the most determined reader.

The labeling should contain a summary of the essential scientific information the physician needs to use the bacterial vaccine or toxoid safely and effectively in the care of patients. It should be informative, accurate and nonpromotional in tone.

Labeling should be reviewed and revised as necessary at intervals of no more than every two years. The date of last revision should be clearly identified in the label. Although the area of bacterial vaccines and toxoids has not been marked by rapid and dramatic advances resulting from medical research, immunization practices do evolve gradually with time and in the light of new data or circumstances. Many of the recommendations contained in the labeling of products currently on the market are out of step with current practice and recommendations. Bibliographic citations should similarly be revised and updated at intervals of no more than every two years.

Labeling should ordinarily contain information in the following format and order:

Description

Clinical Pharmacology/Biological Activity

Indications and Usage

Contraindications

Warnings

Precautions

Adverse Reactions

Overdosage

Dosage and Administration

How Supplied

The Panel has reviewed and concurs with the proposed format changes as described in the statement on "Labeling of Prescription Drugs Used in

Man" (21 CFR, Parts 1 and 3), previously circulated by the Food and Drug administration. The following comments presume the adoption of these new standards, follow the same recommended format, and reflect our particular concerns in the labeling of bacterial vaccines and toxoids.

Description

This should be a concise statement of the method of preparation of the product, the characteristics of strain or species used, the scientific name of the bacterium, noting the specific strain if important, the process used, the potency standard that has been met, the antigenic content of the product, the stabilizers and preservatives included, and the suspending menstruum. Terms such as "purified" and "refined" are more promotional than scientifically meaningful. An accurate statement of the precise process that is used would be considerably more meaningful.

Clinical Pharmacology/Biological Activity

This section should contain a concise factual summary of the immunological response to the product in terms of immunity, antibodies or other parameters. Specific points to be covered, when applicable include: The proportion of individuals in which antibody will be produced, the number of doses required to produce satisfactory levels of antibody, techniques and reliability of antibody measurements, the time at which antibody is detectable, peak antibody levels to be expected, expected decay of antibody titers, and the degree and duration of protection to be expected. Concise summary description of data in support of the efficacy of the product in animals or in man should also be included.

## Indications

The indications should be stated as specifically as possible. Liberal use should be made of the recommendations of official bodies such as the Public Health Service Advisory Committee on Immunization Practices, Center for Disease Control, the Infectious Disease Committee of the American Academy of Pediatrics, and the American Public Health Association. The specific recommendations of these advisory groups should, if appropriate, be reprinted in their entirety in the labeling. The number and frequency of injections of a given antigen(s) should be specifically stated. If products containing more or fewer antigens as combined products (e.g., DT, DTP) are preferred for a specific purpose, this should be so stated in this section. In such a case, the circumstances should also be defined when the product under consideration should be used rather than the preferred product. Where appropriate, labeling should also point out the generally accepted superiority of adsorbed vaccines and toxoids over comparable fluid products.

## Contraindications

This section should state those situations in which the agent should not be used because the risk of use clearly outweighs any possible benefit. Such situations include administration of the agent to patients known to have a serious hypersensitivity to it and use of the agent in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it or not receiving the expected benefit from it. This

section should list known hazards, and theoretical hazards, if mentioned, should be identified as such. The Panel encountered in their review a number of labels in which it appeared that producers were overly concerned about protecting themselves, rather than the patient.

Warnings

This section should state serious adverse reactions and potential safety hazards, limitations of use imposed by them, and steps which should be taken if they occur. This section should describe any unusual circumstances relating to the use of the product, including particularly any circumstances under which use of the product may be hazardous or less effective. The specific circumstances and the specific hazards should be described fully.

Precautions

This section should contain the following subsections as appropriate for the product;

1. General. This subsection should list any special care that should be exercised to permit safe and effective use of the product by the physician.

2. Clinical and laboratory tests. This subsection should list those laboratory tests which may be needed to follow the patient's response or to identify possible adverse reactions.

3. Special instructions to be given the patient. This subsection should specify instructions for patients to achieve safe and effective

use. Any patients' brochure or printed instructions to vaccinees should be reprinted under this section heading.

4. Clinically significant product interactions. This subsection should provide specific practical guidance to the physician on avoiding and/or managing clinically significant drug interactions, such as might occur with simultaneous active-passive immunization.

5. Pregnancy. Recommendations concerning the use of the product during pregnancy should be detailed in this section.

Adverse Reactions

This section should contain not only a description of the nature of local and systemic adverse reactions that have been observed following use of the product as recommended, but also their relative frequency. Specific recommendations for management of adverse reactions should also be included in this section, as should recommendations for reporting of adverse reactions to the manufacturer and the Food and Drug Administration.

Overdosage

This section should describe the signs, symptoms, and laboratory findings of accidental overdosage and the general principles of management. It should include specific information, if available, on the emergency treatment, antidotes, and the value of any recommended therapeutic measures.

Dosage and Administration

This section should state the usual recommended dose and frequency, and if appropriate, limits beyond which the product should

not be administered. Precautions against inadvertent intravenous injections should be included. It should include the intervals recommended between doses, and modification of dosage needed in special patient populations such as infants and children. Specific tables or nomograms should be included to clarify dosage schedules. This section should also contain specific directions on dilution, preparation, and administration of the product if needed, and storage conditions for stability of the product where important.

How Supplied

This section should state the available dosage forms, potencies, and units of issue of each product to which the labeling is applicable.

## GENERIC STATEMENT ON REQUIREMENTS FOR A WELL-CONTROLLED FIELD TRIAL

Some of the immunizing agents the Panel was required to evaluate had been tested for efficacy only in the first part of the 20th century, when the methodology for obtaining unbiased reliable results in field trials had not yet been fully worked out. Examples of such agents are diphtheria and tetanus toxoids. The respective diseases have declined in incidence, and opportunities for additional field testing for efficacy do not exist in this country.

In developing new immunizing agents, the products are generally first tested in animals for their toxicity and ability to elicit antibody response. When the animal model is suitable, the protection provided by immunization against challenge by the microorganism is also evaluated. Subsequently the immune response in humans is measured, and the dose which induces a seemingly adequate immune response with an acceptable low rate of adverse reactions, is sought.

The final and most important step is the field trial, when a large number of presumably nonimmune humans are inoculated, and the incidence of the disease among vaccinees and control subjects is compared.

In the past "historical" controls were frequently employed to test the effects of a new vaccine. By this no longer acceptable technique, the frequency of illness in a vaccinated group was compared to the frequency in a similar unvaccinated population at some time in the past. Unfortunately, a decline in disease frequency after vaccination cannot

be interpreted as resulting from vaccination, because the changes may be due to natural disease cycles, to changing socioeconomic conditions or to therapeutic measures, such as antibiotics.

Also no longer acceptable are comparisons of the frequencies of disease in those who do and do not volunteer for a vaccine study. The fallacy of this approach is that volunteers differ from nonvolunteers in many important aspects. For instance, the former may be more health conscious and inclined towards prevention; they may come from smaller families and living conditions may differ from those of nonvolunteers. Such behavioral and socioeconomic factors may effect the risk of exposure and the host's natural ability to resist infection. Modern scientific methodology requires that volunteers for a study be divided into groups by a randomization procedure, one group constituting the control group, which is given a placebo (inactive, dummy) substance. Randomization is necessary to ensure, that the volunteers are distributed without bias, thereby increasing the chances that all variables, known and unknown, that might affect the results of the study are distributed evenly between vaccinated and control groups. Indeed, if the populations are heterogeneous in age, sex, race or other important variables, it may be necessary to classify or "stratify" them into groups according to these characteristics with randomization within these groups. These rigidly designed experiments, with or without stratification, are called "controlled trials."

An additional requirement in a controlled trial is that the study be carried out double-blind if at all feasible. This implies that both

the study subjects and the observers are unaware of the treatment assigned to the individual, in order to insure unbiased assessment of outcome.

Before subjects are enrolled in controlled trials, ethical considerations require that all the procedures in the studies are explained to them, and that the risks as well as possible benefits are adequately described. The right to withdraw from the study at any time without penalty is pointed out. The rights of the subjects are protected by special committees in all major research centers and by special committees at the Department of Health, Education, and Welfare. These committees review the applicable consent forms and the research. All government sponsored research and virtually all other research involving human subjects requires review by institutional human subjects rights committees.

Whenever practical, in order to provide some benefit to the control group, a vaccine against an entirely different disease, rather than an inactive placebo, is given to the control group.

Assignment to groups is carried out after the subjects have decided on participation, and after the study has been fully explained to them. Participation of children requires special consideration. Consent from parents as well as older children must be obtained.

In carrying out controlled field trials of new improved vaccines, ethical considerations do not allow a placebo assignment if an effective vaccine already exists. Thus, comparison can only be made between those given the new and the old product; enrollment of very large population groups may be necessary in order to distinguish small differences in efficacy.

Analysis of the results of a vaccination study is achieved by "breaking the code" identifying the allocation of individuals to vaccinated or control groups. The code is broken at the end of the study or after an outbreak of the disease has occurred. Under some circumstances it may be desirable for a statistician, who possesses the allocation code but is not participating directly in the study, to examine periodically the results as they accumulate. By this mechanism, called sequential analysis, the study can be interrupted as soon as it has become evident that one treatment or vaccine is superior to the other.

Field trials designed to measure efficacy directly have become increasingly difficult to conduct under conditions of decreasing incidence of natural disease. For this reason, serologic documentation of efficacy must increasingly be substituted in lieu of direct evidence of efficacy. The following protocol is provided to serve as an example of one type of serologic study which would provide reliable information on the efficacy of the product to be assayed as simply and as economically as possible and is illustrative of many of the concepts implicit in the Panel's position regarding well-controlled field trials as well as in the Food and Drug Administration's regulations regarding such matters (see 21 CFR 314.111):

SAMPLE PROTOCOL FOR ASSAYING

EFFICACY OF TETANUS TOXOID IN MAN

Objective. To determine by a study with the fewest number of subjects and fewest number of bleeds required whether a particular preparation

of Tetanus Toxoid (alone or combined with Diphtheria Toxoid) produces an acceptable level of immunity in individuals not previously inoculated with Tetanus Toxoid. An acceptable level of immunity is defined as:

1. Over 80 percent of subjects having $\geq$ 0.01 international unit of Tetanus Antitoxin per ml in a serum sample drawn 10-14 days after basic immunization (2 injections of adsorbed Toxoid or 3 of fluid Toxoid) have been given. OR

2. Over 80 percent having $\geq$ 0.1 international unit per ml in serum sample drawn 10-14 days after a reinforcing injection given 6 to 12 months following basic immunization as defined above.

It is to be noted that 80 percent "success" by either criterion given above is a minimum tolerated level; the normal success rate, in many studies reported over the last 3 decades, is 95-100 percent.

Subjects. The study population should consist of healthy children or adults of either sex, and should have acceptable evidence of being primary responders to tetanus toxoid. In the case of infants less than 6 months of age, negative immunization

history from a responsible parent or guardian would be considered acceptable. For older children and adults, the most valid evidence of primary response is the absence of serum antitoxin seven days after the initial dose of toxoid. In neither instance is a preimmunization serum necessary. Data from older children and adult subjects screened for antitoxin negativity by a 0-day rather than a 7-day bleeding may be confounded by the inadvertant inclusion of individuals who are secondary rather than primary responders.

Numbers. Size of group should be so selected as to provide serological data on 40 acceptable subjects at end of study. Sixty is recommended as a minimum starting number if subjects can be carefully selected by good histories of no prior Tetanus Toxoid injections (about 10-20 percent will have had previous toxoid injections without their knowledge). However, larger samples, if possible, would be desirable and might provide more data. Another 10-20 percent may be expected to drop out of the study along the way.

Evaluation. On a 95 percent probability basis, US MIL-STD 105D (Canadian Standard CA-C-115; "Specification for Sampling Procedures and Tables for

Inspection by Attributes," British Standards Institution, BS 6001, 1972), indicated that the following 2-sample sequence may be used to obtain an answer:

| | Accept | Reject |
|---|---|---|
| 1st sample of 20 | 1 failure | 4 failures |
| for 2 or 3 failures, go to: | | |
| 2nd sample of 20 | 4 failures | 5 failures |
| (Total of 40) | | |

## ACTIVE IMMUNIZATION PRODUCTS

### Generic Statement on Diphtheria Toxoid

Diphtheria is an infectious and communicable disease of man which usually involves the upper respiratory tract and sometimes produces skin infections. The causative agent is Corynebacterium diphtheriae, a gram-positive bacillus with metachromatic granules. Upper respiratory diphtheria is characteristically associated with the production of a pseudomembrane in the nasal passages, pharynx, and/or larynx, and with the appearance of systemic symptoms due to adsorption of an exotoxin. Fifty years ago there were approximately 200 cases per 100,000 population in the United States each year (roughly 350,000 cases annually). This has decreased to a rate of about 0.1 per 100,000 population in recent years (200 to 400 cases annually). Approximately 10 percent of patients with diphtheria succumb. Death may be due to respiratory obstruction by the membrane or to remote effects of the toxin upon the myocardium or peripheral nervous system.

Because the morbidity and mortality of diphtheria are largely a consequence of the toxin elaborated by the organism, antiserum (antitoxin) prepared by immunizing horses has been used for nearly 80 years in the treatment of the disease and for its prevention in exposed, susceptible individuals. This approach to control of the disease is only partially successful, because the disease is already well established by the time it is recognized, and toxin that has been adsorbed and fixed to cells is unaffected by antitoxin.

Further, antitoxin does nothing to prevent spread of disease. Penicillin or other effective antibiotic agents will usually eradicate the organism but, because they have no effect against toxin, antibiotics are only an adjunct to therapy.

Since passive immunization with antitoxin and therapy with antimicrobial agents do not provide a satisfactory approach to the control of diphtheria, active immunization of humans against the toxin has been employed for many years (also see Generic Statement on Diphtheria Antitoxin). The reduction in morbidity and mortality from diphtheria in the United States during the past half century is largely attributable to widespread immunization against the toxin.

## Description

Diphtheria toxoid is a cell-free preparation of diphtheria toxin treated with formaldehyde so that, when administered to humans, it does not produce the known toxic effects of diphtheria toxin but nonetheless produces a specific immune response to the toxin.

The rationale for this preparation is based on the fact that the pathogenicity of the Corynebacterium diphtheriae for man is almost entirely derived from the effects of its exotoxin. Rarely, apparently nontoxin producing strains of the organism produce disease. Also uncommon is disease produced by toxigenic strains in individuals immune to the toxin. In these rare instances, the significance of the disease is dependent upon local inflammatory response, and not upon systemic dissemination of toxic products.

Early in this century, attempts were made to devise means by which immunity to the toxin might be induced in man. The potency of the toxin is such that the miniscule amounts that can be safely administered to man fail to induce protection. Indeed, the disease itself sometimes fails to induce immunity in survivors. The first successful preparation for inducing immunity was a balanced combination of diphtheria equine antitoxin and the toxin. Disadvantages included reversion to toxicity when frozen, frequent sensitization to horse serum and less than optimum induction of the immune state.

Attempts to detoxify the toxin without destroying its antigenicity repeatedly failed because of the instability of the toxoid, until it was shown that formaldehyde treatment of the toxin produced the desired result. Current toxoids are a result of this observation.

Combinations of the formaldehyde inactivated toxoid with various aluminum compounds have resulted in preparations more antigenic than the fluid (plain) toxoid, and represent the most commonly used preparations in the United States. Such preparations are designated "adsorbed."

## Production

A strain of Corynebacterium diphtheriae established as a potent toxin producer, is grown in a liquid medium so constituted as to afford optimum conditions for toxin production. The medium must be free of blood products, horse or other animal serum, and any proteins known to be allergenic to man. Removal of bacterial cells and sterilization are accomplished by centrifugation and filtration. The resultant toxin is

tested for potency according to the United States standards and is incubated with formaldehyde in established proportions to effect conversion to toxoid. Before or after conversion to toxoid, additional steps are usually taken to partially purify and concentrate the fluid antigen.

Treatment of the fluid toxoid with aluminum compounds is employed utilizing established techniques to produce the adsorbed product. A preservative (usually thimerosal but never phenol) is added.

The amounts of toxoid present in preparations are specified in flocculation units (Lf), measured by established techniques.

Use and Contraindications

This product, used for active immunization against diphtheria, is rarely indicated as a single toxoid, either in the fluid or adsorbed form. For primary immunization of children younger than 7 years of age, it should almost always be used in a combined product with tetanus toxoid and pertussis vaccine. Poliomyelitis vaccine consisting of inactivated poliovirus may be included as a fourth antigen, but live, oral, poliovirus vaccine, consisting of attenuated virus is currently preferred for poliomyelitis immunization in the United States. The triple antigen products are preferred over monovalent diphtheria toxoid not only because of efficiency and economy but also because pertussis vaccine enhances the immunogenicity of the toxoids (adjuvant effect). Also, the adsorbed products are more antigenic than the fluid products and the antitoxic immunity is of longer duration.

Thus, it is strongly recommended that routine immunization of children under 7 years of age against diphtheria be accomplished by the use of combined adsorbed diphtheria and tetanus toxoids and pertussis vaccine (DTP), according to schedules recommended by the Public Health Service Advisory Committee on Immunization Practices of the United States Public Health Service, the American Academy of Pediatrics and the American Public Health Association. These advisory bodies also recommended the use of adsorbed combined tetanus and diphtheria toxoids of the adult type (Td) for primary immunization of children older than 6 years and adults. However, the efficacy of Td as a primary immunizing agent against diphtheria has not been firmly established. (See Special Problems, Number 1, diphtheria toxoid generic statement.)

In the unusual instances in which primary immunization with monovalent diphtheria toxoid is indicated, the adsorbed form is preferable. Primary immunization with adsorbed toxoid comprises three doses, 2 given 4 to 8 weeks apart, and the third dose (reinforcing) 1 year later. Booster doses should probably be given 5 years after the primary three doses and again after an interval of approximately 10 years. (See Special Problems, Number 1, diphtheria toxoid generic statement.) In children older than 6 years and adults the booster doses should probably be given as one-fifth of the usual dose or as Td because of an increased likelihood of reactions. Monovalent diphtheria toxoid may be used for booster doses in the presence of an outbreak of diphtheria, but usually under these circumstances advantage should be taken of the opportunity to enhance tetanus immunity by the use of Td.

If the fluid toxoid is used, primary immunization should include 4 doses, 3 doses 4 to 8 weeks apart, and a fourth dose 1 year later. Booster doses should be given as with the adsorbed preparation.

The fluid toxoid may be administered subcutaneously or intramuscularly. The adsorbed toxoid is preferably administered intramuscularly.

Absolute contraindications to the use of diphtheria toxoid are virtually nonexistent. Apparent anaphylactic reactions to diphtheria toxoid have been rarely reported. A marked febrile response to an injection should be cause for reducing the subsequent dose to one-tenth or one-fifth the former dose. Individuals receiving corticosteroids or other immunosuppressive drugs may not display an optimum immunologic response; accordingly, if discontinuation of such drugs is anticipated within the immediate future, immunization should be delayed until that time. In the presence of a febrile illness it is advisable not to administer diphtheria toxoid alone or in combination with pertussis vaccine because of possible confusion as to the cause of further fever.

Inasmuch as clinical diphtheria may not induce adequate active immunity, immunization of individuals who have recovered from diphtheria and who remain Schick-test positive should be undertaken employing a reduced initial dose because of possible sensitivity.

## Safety

Fluid and adsorbed diphtheria toxoid must be tested to ensure sterility, the absence of free toxin, and the absence of blood group substances in significant amount. All of these tests are well defined

and described by the Bureau of Biologics. Experience with the administration of millions of doses has shown that life-threatening reactions to this toxoid are extremely rare. Transient local reactions and systemic symptoms, primarily fever, are frequent, especially in individuals sensitized by prior exposure to the toxin or toxoid. These reactions are not life-endangering and usually persist only a day or two. The severity of these reactions is directly proportionate to the amount of toxoid administered.

Manufacturers are required to record all reported reactions.

## Efficacy

Although controlled studies employing currently acceptable design methodology and statistical analysis have not been carried out, extensive experience in many countries has shown that the systematic use of this product for the immunization of infants and children has been associated with a striking reduction in the incidence of the disease. Similar but less extensive experience indicates comparable effectiveness in older age groups.

The potency of diphtheria toxoid prior to administration to humans is tested in guinea pigs, and standard procedures for such testing have been developed and are required of manufacturers by the Bureau of Biologics. In the case of the fluid toxoid, each lot must be tested by immunizing guinea pigs, followed by subsequent challenge with toxin to show protection. Unimmunized control animals must be employed to ensure the lethality of the toxin used to challenge the immunized animals.

Adsorbed diphtheria toxoid is tested by immunizing guinea pigs and subsequently determining diphtheria antitoxin levels as prescribed.

Quantitative correlation, however, between the results of animal protection tests and primary immunogenicity in man has not been established, although it is assumed that there is a direct relationship. For primary immunization, direct testing of antitoxin response in man should be required, and should be repeated whenever significant changes in the manufacturing process are made. However, past experience indicates that all toxoids which meet the Bureau of Biologic's requirements for potency in animals have proved effective as boosters in man. (See Special Problems, Number 3, Diphtheria Toxoid Generic Statement.)

Because field testing of disease prevention is currently not feasible, testing for efficacy in man requires evaluation of the induction of serologic immunity. This may be achieved by serological tests, or by the performance of the Schick skin test which reflects serologic and clinical immunity with satisfactory accuracy. Three doses of the fluid toxoid, given 4 weeks apart, or 2 doses of the adsorbed preparation, separated by 4 weeks, should result in at least 80 percent conversion of Schick positive or seronegative subjects to the Schick negative state or the seropositivity (0.01 or more units of diphtheria antitoxin per ml of serum) by 1 month after the last dose. To avoid confounding by anamnestic responses, use of the Schick test technique for efficacy testing in man should be limited to young infants clearly receiving primary immunization. Similarly, infants should be used for

serologic testing, or a blood sample should be drawn 7 days after the first dose and tested for evidence of an accelerated immune response which, if absent, would indicate primary immunization.

## Special Problems

Diphtheria toxoid, as an immunizing agent in man, presents several problems that warrant efforts toward solution.

1. Although the safety of different lots of diphtheria toxoid products may be assured by animal testing, no animal model or other laboratory technique for evaluation of effectiveness has been directly correlated with primary immunogenicity in humans with acceptable precision. Titers of antibodies as determined by neutralization of the toxin in experimental animals or in tissue culture systems are better related to immunity than is the presence of hemagglutinating antibodies in serum specimens. However, the presence of low neutralizing titers does not ensure protection against large amounts of toxin.

2. The nonspecific reactogenicity of diphtheria toxoid, probably due largely to extraneous proteins derived from the organisms, represents a complicating factor in the immunization of individuals who have become sensitized to these proteins. The Panel has noted that there are no purity requirements in terms of Lf content per milligram of nitrogen except for the Td product.

3. For several reasons, diphtheria toxoid, fluid or adsorbed, is not as effective an immunizing agent as might be anticipated. First, clinical diphtheria may occur occasionally in immunized individuals--even those whose immunization is reported as complete by recommended

regimens. However, when it does occur in such individuals, it appears to be milder. Second, diphtheria toxoid provides protection only against the toxin and not against the somatic components of Corynebacterium diphtheriae. Occasional local infections, respiratory or cutaneous, may occur in immune individuals and nontoxigenic strains may produce focal infections. Although both of these situations are encountered from time-to-time, they are not of major importance. Third, the permanence of immunity induced by the toxoid in the light of decreasing likelihood of exposure to the organism (the "streetcar booster") is open to question. In the absence of occasional exposure, it is possible that individuals immunized as children will not retain a degree of immunity which will provide adequate protection in later years. Fourth, the smaller amount of diphtheria toxoid present in tetanus and diphtheria toxoids combined for adult use (Td) has never been shown conclusively to be an adequate primary immunizing agent. Furthermore, the intervals between booster doses of Td in adults sufficient to maintain diphtheria immunity have not been established. Fifth, commendable efforts by producers to reduce the nonspecific reactivity of the toxoid by increased purification may have resulted in diminished immunogenicity.

Finally, the absence of proof recently obtained in humans for certain diphtheria toxoids by simple serological tests of readily measurable antibodies could not allow a Category I assignment. (See section 2.b. (2) of the Introduction in this Report.)

Recommendations

The following recommendations for the production, use and evaluation of diphtheria toxoid are made:

1. Of maximum importance is the development of an animal or laboratory testing system that correlates consistently and with acceptable precision with primary immunogenicity in humans. Public funding to support such research should be made available. Until such a model is established, current toxoids and new variations on such toxoids will require field testing in humans employing serologic methods. Such field testing is expensive and difficult to conduct both because of the problem of finding suitable nonimmune subjects and because of the current restraints on research using human beings. Further, the necessity for field testing of each toxoid produced by a new or varied technique would understandably inhibit manufacturers in terms of innovation and improvement, and place a difficult burden upon the Bureau of Biologics in determining which alterations in production methods represent sufficient departures to warrant field testing. Enhanced correlation of existing animal models with immunogenicity in man would obviate such repetitive, time consuming, logistically difficult and expensive field studies.

2. Efforts should be made to reduce nonspecific reactogenicity of the toxoid. Standards should be established for purity of the toxoid in terms of Lf content per milligram of nitrogen.

3. Public support for the development of a more immunogenic toxoid should be considered. Of much lower priority is development of an

immunizing agent against components of the organism other than the toxoid.

Monitoring of the diphtheria immune status of the population by Schick testing or serologic testing would seem to be of maximum importance to prevent the development of a large population at risk in the future. The value of the Schick test is well established. However, the preparation of Schick test material is an understandably unprofitable undertaking for manufacturers. Public support may be necessary for continued production of this material, which is infrequently used but occasionally invaluable.

4. It is recommended that the apparent immunogenic superiority of the adsorbed toxoid over the fluid preparation be strongly emphasized and be included in labeling of products.

5. Finally, for the diphtheria toxoids whose effectiveness can be established by simple blood tests, there must be a resolution of the conflict in public policy between insistence on effectiveness data and constraints on obtaining such data resulting from the complex issue of informed consent. (See section 2.b. (2) in the Introduction to this Report.)

## Basis for Classification

Past experience indicates that all diphtheria toxoids which meet the Bureau of Biologics requirements for potency in animals tests have proved effective as boosters in man. Therefore, all currently licensed and marketed products are classified in Category I as regards their use for secondary or booster immunization.

However, quantitative correlation between primary immunogenicity in man and the results of animal protection tests has not been established; therefore direct testing of antitoxin responses in man is required, and should be repeated whenever significant changes in the manufacturing process are made. For these products, therefore, for which such evidence of effectiveness in primary immunization has not been acquired, Category IIIA is recommended.

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SPECIFIC PRODUCT REVIEWS

Diphtheria Toxoid Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

DIPHTHERIA TOXOID MANUFACTURED BY CONNAUGHT LABORATORIES, LTD.

1. Description. This product contains 40 to 50 Lf fluid diphtheria toxoid per ml. According to a revision of manufacturing procedures in 1973, the current product should contain 50 Lf per ml.

2. Labeling--a. Recommended use/indications. This preparation is recommended for active immunizations against diphtheria. Three doses of 1 cc (50 Lf) each at intervals of 4 weeks, beginning at 3 to 6 months of age. Reinforcing doses of 1 cc are given 1 year after the primary series and 4 years later. At school age an additional reinforcing dose of 0.1 to 0.2 ml may be given without being preceded by a reaction test.

b. Contraindications. Contraindications are not well outlined. Reaction tests are recommended in older children (over 8 years) and adults.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. In studies (Ref. 1) carried out in 1964 to 1965, 68 children, ages 7 to 15 years, were evaluated for their diphtheria antitoxin levels after 3 injections of Connaught Laboratories DT - polio vaccine. Sera from 54 children had no preimmunization antibody, and were considered to be primary responders. Eighty-three percent had protective levels of diphtheria antibody 1 month after the third injection.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No data relating specifically to this product are presented. The manufacturer states that adverse reactions have not been reported.

c. Benefit/risk ratio. The benefit-to-risk assessment of the product is satisfactory.

d. Labeling. There is some inconsistency in labeling in the submission as to exact Lf content. Contraindications should be listed.

4. Critique. This product meets United States standards for animal safety and potency and appears safe in humans. Serologic data show adequate antibody response. The package insert should mention contraindications, and it should be stated that the preferred product for immunizations of infants is a combination product (DTP).

5. Recommendations. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

DIPHTHERIA TOXOID, FLUID MANUFACTURED BY

DOW CHEMICAL COMPANY

1. Description. This manufacturer maintains a license for fluid diphtheria toxoid, although it has apparently never marketed the product as a monovalent antigen, either in the fluid or adsorbed form. Instead, it is supplied in 2 adsorbed products, 1 in combination with tetanus toxoid and the other with tetanus toxoid and pertussis vaccine. Techniques for preparation of the toxoid for ultimate combination meet or exceed Federal requirements.

2. Labeling--a. Recommended use/indications. Nonexistent because the product is not marketed.

b. Contraindications. Nonexistent because the product is not marketed.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements when tested after combination with tetanus toxoid and adsorption.

(2) Human. No data relating directly to this product are available.

b. Safety--(1) Animal. This product meets Federal requirements when tested after combination with tetanus toxoid and adsorption.

(2) Human. No data relating specifically to this product are available. There have been only 5 reports in a 10 year period of reactions to the adsorbed product combined with tetanus toxoid, and all 5 of these were insignificant.

c. Benefit/risk ratio. The benefit-to-risk assessment cannot be determined for this unmarketed product.

4. Critique. The manufacturer maintains a license for diphtheria toxoid, fluid although it has never been marketed in the monovalent form. Inasmuch as the manufacturer does maintain a license for 2 combined forms of adsorbed diphtheria toxoid, the Panel believes that maintenance of this license is superfluous.

5. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

DIPHTHERIA TOXOID MANUFACTURED BY ISTITUTO

SIEROTERAPICO VACCINOGENO TOSCANO "SCLAVO"

No data have been provided by the manufacturer for diphtheria toxoid, for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

DIPHTHERIA TOXOID ADSORBED MANUFACTURED BY ISTITUTO SIEROTERAPICO VACCINOGENO TOSCANO "SCLAVO"

1. Description. A diphtheria toxoid purified by the metaphosphoric acid method, containing 15 Lf of toxoid per 0.5 ml dose, and 2 mg aluminum hydroxide per 0.5 ml dose* (80 percent of maximum permitted amount). It is preserved in thimerosal at a concentration of 1:10,000.

2. Labeling--a. Recommended use/indications. For active immunization against diphtheria in children under 6, two 0.5 ml doses 6 to 8 weeks apart and a "booster" dose 1 year later. There is no discussion concerning choice of this product as against diphtheria toxoid or diphtheria and tetanus toxoids and pertussis vaccine. The container label should say "SHAKE WELL."

b. Contraindications. Acute or active infections and temporary immunosuppression; in situations involving prolonged immunosuppression an extra dose is recommended.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. A "controlled study" (Ref. 2) is cited using this toxoid in combination with typhoid-paratyphoid A and B (TAB) for children all previously immunized against diphtheria. Three to 4-fold increases in antitoxin titer were observed. Additional data submitted on DT and Td provided evidence of effectiveness.

b. Safety--(1) Animal. This product meets Federal requirements.

* The label submitted to the Panel is wrong. This product contains 1 mg of $Al(OH)_3$ per dose. It is the Panel's understanding that the labeling has been corrected.

(2) Human. The lack of complaints or claims against the product suggest that it is presumably not unduly reactive.

4. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

5. Critique. Additional data were provided to the Panel subsequent to the original submission. The data were submitted as part of a license application to the FDA for DT and Td products, but in accordance with the guidelines established by the Panel regarding the extrapolation of data from the use of combined vaccines, there was sufficient information to show that this product is safe and effective.

6. Recommendations. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of the Report.

DIPHTHERIA TOXOID MANUFACTURED BY MASSACHUSETTS PUBLIC HEALTH BIOLOGIC LABORATORIES

1. Description. This is a fluid diphtheria toxoid, which is no longer issued. It contains 20 Lf of diphtheria toxoid per ml. No information on production details is provided. The diluting medium is sodium chloride, buffered with 0.05 M phosphate buffer. The preservative is thimerosal in concentration 1:10,000.

2. Labeling--a. Recommended use/indications. No labeling is included in the submission.

b. Contraindications. No labeling.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Several published reports on the efficacy of the manufacturer's products are cited in the submission (Ref. 3). In the 1950's, this toxoid appeared efficacious in eliciting antitoxin response in persons who did not demonstrate measureable antitoxin in their blood.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Safety data are presented (Ref. 3) from a multitude of publications from the 1950's and 1960's, and suggest that the product is innocuous.

c. Benefit/risk ratio. The benefit-to-risk assessment for this product appears to be satisfactory.

4. Critique. This fluid diphtheria toxoid has been shown to be

safe, and the data from the literature support its efficacy when used as directed for primary immunization. No package insert is provided.

5. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in this country in the form for which licensed.

DIPHTHERIA TOXOID MANUFACTURED BY MERRELL-NATIONAL LABORATORIES, DIVISION OF RICHARDSON-MERRELL INC.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

DIPHTHERIA TOXOID, FLUID MANUFACTURED BY

PARKE, DAVIS AND COMPANY

1. Description. This is a fluid diphtheria toxoid containing 88 Lf of diphtheria toxoid per 0.5 ml dose. The final product contains 0.5 percent glycerin, 1:10,000 thimerosal as a preservative, and is suspended in isotonic sodium chloride. A strain of Corynebacterium diphtheriae PW8 of proven toxigenicity is used for toxin production. Formaldehyde is used as the toxoiding agent, and the toxoid is then further purified by ultrafiltration, ammonium sulfate precipitation, and subsequent dialysis.

This product is not currently on the market, but the manufacturer wishes to retain its license for possible future public health and medical demand.

2. Labeling--a. Recommended use/indications. No labeling was submitted.

b. Contraindications. No labeling was submitted.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal minimum requirements for diphtheria toxoid.

(2) Human. In 1961 to 1962, as part of a combined evaluation of diphtheria and tetanus toxoids, and poliomyelitis vaccine, a total of 61 prison inmates were given a variety of preparations containing Parke-Davis diphtheria toxoid singly or in combination with tetanus toxoid and poliomyelitis vaccine (Ref. 4). In most instances the doses administered probably elicited booster responses. It is not stated, however,

whether fluid or adsorbed toxoids. Furthermore, it was not clear whether the vaccines were experimental lots or the toxoids currently in use.

b. Safety--(1) Animal. This product meets Federal requirements for diphtheria toxoid.

(2) Human. No data were provided to substantiate the safety of this product.

c. Benefit/risk ratio. This cannot be determined in the absence of adequate data with regard to safety and efficacy.

4. Critique. This is a fluid diphtheria toxoid, currently licensed, but not marketed, which appears to meet animal efficacy and safety requirements. Satisfactory data have not been provided by which to assess either the safety or efficacy of this product in humans, whether used for primary or booster immunization.

No labeling has been submitted.

The Panel has a general concern about the present indications for the use of fluid diphtheria toxoid, in view of the greater and more durable immunity provided by adsorbed toxoids.

5. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

DIPHTHERIA TOXOID ADSORBED MANUFACTURED BY

PARKE, DAVIS AND COMPANY

1. Description. This is an aluminum phosphate adsorbed diphtheria toxoid, containing 15 Lf per 0.5 ml dose, and 2.5 mg of aluminum phosphate per 0.5 ml dose. It is suspended in 0.9 percent saline, and 1:10,000 thimerosal is included as a preservative. The manufacturing process, clarified in a supplemental submission defines the strain of Corynebacterium diphtheriae to be used, and outlines a process of ultrafiltration, ammonium sulfate precipitation, and subsequent dialysis. This product is not currently on the market, but the manufacturer wishes to retain its license for possible future public health and medical demand.

2. Labeling--a. Recommended use/indications. This product is said to be recommended for the active immunization of children from 6 months to 8 years of age, where a multiple antigen is not indicated. The labeling further states that this product may be used to immunize older children and adults, but with appropriate caution because of the possibility of reactions.

A complete immunizing treatment is said to consist of two 0.5 ml doses at intervals of 4 to 6 weeks. A recall dose 1 to 2 years after the initial course is recommended for full protection. The labeling was last revised in December 1964, and thus differs strikingly from current national recommendations.

b. Contraindications. No absolute contraindications are listed. Children with a negative Schick test are recommended not to receive diphtheria toxoid.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements for diphtheria toxoid.

(2) Human. In 1961 to 1962, as part of a combined evaluation of diphtheria and tetanus toxoids, and poliomyelitis vaccine, prison inmates were immunized with various combinations of Parke-Davis diphtheria toxoids (Ref. 4). In most instances, the serologic responses obtained apparently represented booster reactions. Furthermore, it is not clear whether the products used were fluid or adsorbed diphtheria toxoid.

b. Safety--(1) Animal. This product meets Federal requirements for diphtheria toxoid.

(2) Human. There is adequate documentation of the safety in humans of Parke-Davis adsorbed diphtheria toxoids, as contained in the submission.

c. Benefit/risk ratio. This cannot be determined with precision, owing to the absence of satisfactory data documenting the efficacy of this product when used as a primary immunizing agent. However, it is likely that the benefit-to-risk assessment would be satisfactory when the toxoid is used as a booster immunizing agent.

4. Critique. Since this product is not currently on the market, the labeling is badly out-of-date, and requires substantial revision in order to conform with current national recommendations for use of diphtheria toxoids. Furthermore, the statement that children with a negative Schick test do not require diphtheria toxoid is inappropriate, inasmuch